Ropes & Gray
Symbol #: GUH-PWO-007
Action Due: Att cited-review reIDS
Deadline(s): 14 May 2005 / 14 Jul 2005 Final

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

Ropes & Gray
Symbol #: GUH-PWO-007
Action Due: Resp. to Written Opinion
Deadline(s): 14 May 2005 / 14 Jul 2005 Final

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

To:
ROPES & GRAY LLP
Attn. Treannie, Lisa M.
One International Place
Boston, MA 02110-2624
UNITED STATES OF AMERICA

Ropes & Gray
Symbol #: GUH-PWO-007
Action Due: File Article 19 Amendment
Deadline(s): 14 May 2005 / 14 Jul 2005 Final

Applicant's or agent's file reference GUH-PWO-007	Date of mailing *(day/month/year)* 14/04/2005
	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US2004/023014	International filing date *(day/month/year)* 16/07/2004
Applicant GEORGETOWN UNIVERSITY	

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

   When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 740.14.35

   For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   [ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   [ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Anu Evers

Ropes & Gray
Intellectual Property Dept.
APR 19 2005

Form PCT/ISA/220 (January 2004) *(See notes on accompanying sheet)*

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims,description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference GUH - PWO - 007	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US2004/023014	International filing date *(day/month/year)* 16/07/2004	(Earliest) Priority Date *(day/month/year)* 18/07/2003
Applicant GEORGETOWN UNIVERSITY		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
      [ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box II).

3. [ ] **Unity of invention is lacking** (see Box III).

4. With regard to the **title,**
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**
   [X] the text is approved as submitted by the applicant.
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings,**
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant.
      [ ] as selected by this Authority, because the applicant failed to suggest a figure.
      [ ] as selected by this Authority, because this figure better characterizes the invention.
   b. [ ] none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/023014

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/574 G01N33/569 C12Q1/68 G01N33/573 C07K14/47
C07K14/79 C07K14/82 A61K48/00 A61K38/00 A61K39/395

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	WO 99/29890 A (DIGENE CORP ; LORINCZ ATTILA T (US)) 17 June 1999 (1999-06-17) p.3, line 14 - p.5, line 15, claims	1,9,17, 60,69-72 2,11,18, 46-52,61
A	WO 02/08764 A (MEDICAL RES COUNCIL ; DOORBAR JOHN (GB)) 31 January 2002 (2002-01-31) claims 1-22	1,24, 46-52, 60-72
X	ANDERSON SUZANNE ET AL: "Telomerase activation in cervical cancer" AMERICAN JOURNAL OF PATHOLOGY, vol. 151, no. 1, 1997, pages 25-31, XP009039570 ISSN: 0002-9440	1,2,17, 18,60, 61,69-72
Y	the whole document	3,12,19, 62

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 November 2004	14.04.05
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Authorized officer Hoesel, H

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X A	WO 02/078695 A (LU TAO ; HURLEY LAURENCE H (US); UNIV TEXAS (US)) 10 October 2002 (2002-10-10) p. 5, lines 12-17, p. 30 lines 13-18	46-52 1-24, 60-72
X	YATABE NORIYUKI ET AL: "2-5A antisense therapy directed against human telomerase RNA inhibits telomerase activity and induces apoptosis without telomere impairment in cervical cancer cells" CANCER GENE THERAPY, vol. 9, no. 7, July 2002 (2002-07), pages 624-630, XP002305238 ISSN: 0929-1903 the whole document	46-52
A		1-24, 60-72
X	DATABASE WPI Section Ch, Week 200260 Derwent Publications Ltd., London, GB; Class B04, AN 2002-563528 XP002305239 & KR 2002 012 838 A (BIOGRAND CO LTD) 20 February 2002 (2002-02-20) abstract	1,9,17, 60
A	VELDMAN TIM ET AL: "Human papillomavirus E6 and Myc proteins associate in vivo and bind to and cooperatively activate the telomerase reverse transcriptase promoter." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, vol. 100, no. 14, 8 July 2003 (2003-07-08), pages 8211-8216, XP002305412 ISSN: 0027-8424 the whole document	1-24, 46-52, 60-72
Y	BERGER ALLISON J ET AL: "Insulin-like growth factor-binding protein 3 expression increases during immortalization of cervical keratinocytes by human papillomavirus type 16 E6 and E7 proteins" AMERICAN JOURNAL OF PATHOLOGY, vol. 161, no. 2, August 2002 (2002-08), pages 603-610, XP002305413 ISSN: 0002-9440 abstract,p. 607/608, IGFBP-3 expression in clinical samples	3,12,19, 62

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/023014

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 46-52 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

[ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

See annex

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1,3-10,12-17,19-24,60,62-72 (part.); 2,11,18,46-52,61

diagnostic combinations comprising telomerase/hTERT as primary diagnostic marker; treatment of cervical cancer by way of targeting telomerase/hTERT

---

2. claims: 1,2,4-11,13-18,20-24,60,61,63-72 (part.); 3,12,19,53-59,62

diagnostic combinations comprising IGFBP-3 as primary diagnostic marker; treatment of cervical cancer by way of targeting IGFBP-3

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3. claims: 1-3,5-12,14-19,21-24,60-62,64-72 (part.); 4,13,20,31-37,63

diagnostic combinations comprising transferrin receptor as primary diagnostic marker; treatment of cervical cancer by way of targeting transferrin receptor

---

4. claims: 1-4,6-13,15-20,22-24,60-63,65-72 (part.); 5,14,21,38-45,64

diagnostic combinations comprising beta-catenin as primary diagnostic marker; treatment of cervical cancer by way of targeting beta-catenin

---

5. claims: 1-5,7,8,17-21,23,24,60-64,66-72 (part.);6,9-16,22,25-30,65

diagnostic combinations comprising Myc-HPV E6 interaction as primary diagnostic marker; treatment of cervical cancer by way of targeting Myc-HPV E6 interaction

---

6. claims: 1-6,8-14,16-22,24,60-65,67-72 (part.);7,15,23,66

diagnostic combinations comprising HPV E7 as primary diagnostic marker

---

7. claims: 1-7,9-15,17-23,60-66,68-72 (part.);8,15,24,66

diagnostic combinations comprising telomer length as primary diagnostic marker

---

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/023014

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9929890 A	17-06-1999	AU 748022 B2	30-05-2002
		AU 1723299 A	05-07-1999
		AU 746061 B2	11-04-2002
		AU 1911799 A	28-06-1999
		BR 9814271 A	20-03-2001
		BR 9814272 A	03-10-2000
		CA 2313483 A1	17-06-1999
		CA 2313641 A1	24-06-1999
		EP 1038029 A2	27-09-2000
		EP 1038022 A2	27-09-2000
		JP 2001526045 T	18-12-2001
		JP 2002508190 T	19-03-2002
		NO 20002979 A	09-08-2000
		NO 20002980 A	08-08-2000
		WO 9931273 A2	24-06-1999
		WO 9929890 A2	17-06-1999
		US 2003091992 A1	15-05-2003
		US 2001051364 A1	13-12-2001
		US 2002127545 A1	12-09-2002
		US 6355424 B1	12-03-2002
WO 0208764 A	31-01-2002	AU 4087701 A	05-02-2002
		CA 2417075 A1	31-01-2002
		EP 1305631 A1	02-05-2003
		WO 0208764 A1	31-01-2002
		JP 2004505247 T	19-02-2004
		US 2003219726 A1	27-11-2003
WO 02078695 A	10-10-2002	WO 02078695 A1	10-10-2002
		US 2003105130 A1	05-06-2003
KR 2002012838 A	20-02-2002	NONE	

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/023014	16.07.2004	18.07.2003

International Patent Classification (IPC) or both national classification and IPC
G01N33/574, G01N33/569, C12Q1/68, G01N33/573, C07K14/47, C07K14/79, C07K14/82, A61K48/00,

Applicant
GEORGETOWN UNIVERSITY

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Hoesel, H

Telephone No. +49 89 2399-8693

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/023014

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/023014

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

claims Nos. 46-52

because:

☐ the said international application, or the said claims Nos. 46-52 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/023014

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1,3-10,12-17,19-24,60,62-72 (in part); 2,11,18,61

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-24,50,60-62
	No:	Claims	46-49,51,52
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-24,46-52,60-72
Industrial applicability (IA)	Yes:	Claims	1-24,60-72
	No:	Claims	

2. Citations and explanations

   see separate sheet

The following documents have been taken into account during examination:

D1: WO-A-99/29890
D2: WO-A-02/08764
D3: Anderson. S. et al, Am- J. Pathol. vol. 151/1, 1997, p. 25 - 31
D4: WO-A-02/78695
D5: Noriyuki Y. et al, Cancer Gene Therap. vol. 9, 2002, p. 624 - 630
D6: DATABASE WPI Section Ch, Week 200260 Derwent Publications Ltd., London, GB; Class B04, AN 2002-563528 XP002305239 & KR 2002 012 838 A (BIOGRAND CO LTD) 20 February 2002 (2002-02-20)
D7: Veldman T. et al, PNAS, vol. 100, 08.07.03, p. 8211-8216
D8: Berger A. et al, Am. J. Pathol., vol. 161/2, 2002, p. 603-610

SECTION III:

1. Claims 46-52 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

SECTION IV:

2. The common inventive concept linking together the various alternatives listed in claim, is the provision of a method for the diagnosis of cervical cancer based on the detection of at least two biomarkers. This generic concept as well as the selection of primary biomarker is neither new nor inventive in view of the state of the art: D1 for instance discloses diagnostic assays based on the detection of one or more nucleic acids selected from HPV E6 (participating in E6-Myc interaction, cf. claims 1, 3, 6); D2, pertains to the detection of papilloma virus associated biomarkers (E4, E6 or E7) with cell proliferation markers, e.g. CDC6, MCM2, MCM3, MCM4, etc. (cf. D2 claims 1 - 4, 6, 10, 12, 13, 18); D3 discloses that telomerase may serve as diagnostic marker for cervical neoplasia, independent of the known HPV marker E6, und thus renders obvious the combination of E6 (participating in E6-Myc interaction) and telomerase (D3, abstract. p. 27/28, Results). D6 discloses diagnostic kits designed

for the combined detection of HPV16/18 E6 (cf. item 3.1 below) and E7 proteins and MCM5,

Independent claims 25/30, 31/37, 38/45, 46/52 and 53/59 not recite the concept of combination. Thus, neither the combination concept nor the selection of the primary biomarker can provide a common inventive concept within the meaning of Rule 13.2 PCT linking together the various combinations covered by claim 1. Treatment of cervical cancer by means of targeting one biomarker associated with the malignancy is already known. D4 and D5, for instance, disclose treatment of cervical neoplasia by means of inhibition of telomerase activity by administration of specific c-myc/telomerase inhibitors (D4, abstract, claims 54, 55, p. 30, lines 13 - 1) or antisense nucleic acids (D5, abstract and the paragraph extending between pages 629 and 3630).

No other common or corresponding technical features could be identified that establish a common concept linking together the various diagnostic combinations or the various inventive therapeutical approaches. Consequently, the application is considered to contain seven separate groups of inventions based on the choice of the primary diagnostic marker/therapeutical target as identified in the international search report.

The applicant chose not to pay additional search fees. Consequently, the search has been limited to the first invention identified in the claims, i.e. diagnostic combinations comprising telomerase/hTERT as primary diagnostic and therapeutical biomarker.

SECTION V:

3. Treatment of cervical cancer by way of targeting and inhibiting telomerase expression or activity is already known. D4 describes therapeutical inhibition of telomerase activity by core-modified porphyrin derivatives, D5 pertains to an antisense approach to inhibit hTERT expression.
   Thus D4, anticipates the subject-matter of claims 46, 51 and 52, D5, anticipates the subject- matter of claims 46-49, 51 and 52 (Art. 33(2) PCT). The subject-matter of claim 50 is considered to be a priori obvious in view of D4 or D5 (Art. 33(3) PCT).

A particular technical teaching going beyond common and per se trivial assumptions is missing. Thus, the subject-matter of claims 46 - 52 additionally lacks substantial support contrary to Art 6 PCT.

1. Diagnostic methods comprising detection of hTERT and at least one of the further biomarkers listed in claim 1.

4.1. What does myc-E6 interaction mean?
Having regard to D7, no HPV E6 dependent molecular alterations of c-myc have yet been identified. The application does not provide a supported disclosure going beyond this state of the art. Thus, it seems that E6 activates hTERT promoter and increases hTERT expression by coassociation with c-myc. Thus, in the absence of identifiable structural changes of Myc, the relevant marker to be assay for in Myc-E6 interaction is HPV E6 itself.

4.2. According to D3, telomerase is a marker for cervical cancer independent of HPV E6/E7. HPV E6 (as part of the E6-myc interaction) and E7 have been used alone or in combination with other biomarkers in the diagnosis of cervical cancer (cf. D1; D6, both disclosing methods based on analysis of the status of HPV E6 and E7) in view of the disclosure of D3 a skilled person would regard the combination of hTERT as diagnostic biomarker with the known biomarkers E6 and or D7 as obvious, particularly as an increase of sensitivity could be expected.

Thus, the method according to claims 1, 2, 6, 7, 9 - 11, 15, 17, 18, 22, 23, 60, 61, 65, 66 and the kit according to claims 69 - 72 is considered to lack an inventive step in view of D3 alone when taken in combination with D1 or D6.

4.3. Insulin-like growth factor binding protein 3 (IGFBP-3), transferrin receptor, beta catenin, c-myc and telomer length appear to have been known before the effective date of this application as markers for cervical cancer as set out in the description or D8 being involved in the development of cervical cancer.

In this instance the inclusion as diagnostic biomarker appears to be primarily obvious. Particular advantages or significance associated with the choice of one or more of

these markers has not been demonstrated.

Consequently, claims 3 - 5, 8, 12 - 14, 16, 19 - 21, 24,62 - 64, 67 and 68 seems to lack an inventive step, contrary to Art. 33(3) PCT.